Activated Kras Alters Epidermal Homeostasis of Mouse Skin, Resulting in Redundant Skin and Defective Hair Cycling.

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Public Summary:
The hair follicle can remade multiple times during the normal life of a human and is a model of a regenerating organ. Genetic and acquired diseases in humans disrupt this regenerative process, resulting in hair loss. In a group of rare childhood diseases called RAS/MAPK syndromes, premature hair loss is frequently seen, but the mechanisms are unknown. In this study, a RAS mouse model was generated, and the mechanisms of hair loss were identified. Overactive RAS inhibited activation of stem cells in the hair follicle, blocking the normal regenerative process. Surprisingly, we found that the stem cells themselves were not abnormal and conclude that surrounding changes in the hair follicle play a role in keeping the hair stem cells refractory to stimulation and blocks regeneration.

Scientific Abstract:
Germline mutations in the RAS-mitogen-activated protein kinase (RAS/MAPK) pathway are associated with genodermatoses, characterized by cutaneous, cardiac, and craniofacial defects, and cancer predisposition. Whereas activating mutations in HRAS are associated with the vast majority of patients with Costello syndrome, mutations in its paralog, KRAS, are rare. To better understand the disparity among RAS paralogs in human syndromes, we generated mice that activate a gain-of-function Kras allele (Lox-Stop-Lox (LSL)-Kras(G12D)) in ectodermal tissue using two different Cre transgenic lines. Using Msx2-Cre or ligand-inducible keratin 15 (K15)-CrePR, the embryonic effects of activated Kras were bypassed and the effects of Kras(G12D) expression from its endogenous promoter were determined. We found that Kras(G12D) induced redundant skin, papillomas, shortened nails, and hair loss. Redundant skin was associated with basal keratinocyte hyperplasia and an increase in body surface area. Paradoxically, Kras(G12D) also prevented hair cycle activation. We find that Kras(G12D) blocks proliferation in the bulge region of the hair follicle, when activated through Msx2-Cre but not through K15-CrePR. These studies reveal that KRAS, although infrequently involved in RAS/MAPK syndromes, is capable of inducing multiple cutaneous features that grossly resemble human RAS/MAPK syndromes.Journal of Investigative Dermatology advance online publication, 14 October 2010; doi:10.1038/jid.2010.296.